PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Maintenance therapy with proton pump inhibitors and risk of gastric cancer: a nationwide population-based cohort study in Sweden
AUTHORS	Brusselaers, Nele; Wahlin, Karl; Engstrand, Lars; Lagergren, Jesper

VERSION 1 – REVIEW

REVIEWER	Helge L. Waldum Department of Gastroenetrology and Hepatology, St.Olavs Hospital Prinsesse Kristinas Gate 6, 7006 Trondheim Norway No Competing Interest
REVIEW RETURNED	10-Jun-2017

GENERAL COMMENTS	In the present epidemiological study based upon Swedish registers the authors found increased frequency of gastric cancers in patients having been taking PPIs for at least six months during a 7 year period. The strength of the study is the large sample, the robustness of the registers and consistency of the results in subgroups and the total material. It is notable that the increase in gastric cancer is particularly marked in young patients. In this context it should be recalled that gastric cancers of diffuse type in contrast to the intestinal type s not in decline and in US even has been reported to be increased in young people. The authors suggest that obesity causing gastritis could be the cause of the increase in young persons. This is at best speculative. Table 3 showing lower increase in risk the longer the patient had taken PPI is difficult to understand and in some way makes it difficult to accept the total results? Moreover, gastric cancer is primarily a disease of older people, so it is remarkable that PPIs should induces gastric cancer after such a short period? It should be recalled that gastric carcinoids (no called gNETs) and gastric cancer first developed after more than 20 years in persons borne with defect protonpump due to a mutation (Calvete et al. Human Mol Genet 2015; 24:2914-2922). Furthermore, this manuscript does not mention animal studies. It has been known for more than 30 years that profound inhibition of gastric acid secretion in rodents induces gastric tumours of variable malignancy (Havu N. Digestion 1986; 35(Suppl.1):42-55 and Poynter D et al. Gut 1985; 26:1284-1293). Secondary hypergastrinemia leading to ECL cell hyperplasia has been accepted as the mechanism for tumourigenic effect. ECL cell differentiation in human gastric carcinomas has been described in gastric carcinomas in general (Waldum et al.

	Cancer 1998; 83; 435-444) and in the signet ring subtype in particular (Bakkelund K et al. J Histochem Cytochem 2006; 54: 615-621). These facts should be taken into the discussion. In general, the mechanisms of PPIs carcinogenic effect should be discussed. Nevertheless, this study should be accepted after corrections, due to the widespread use of PPIs and the consistent finding in this study.

REVIEWER	Dr. Leonardo Henry Eusebi Department of Medical and Surgical Sciences, University of Bologna, Italy
REVIEW RETURNED	15-Aug-2017

GENERAL COMMENTS	I read with interest the work by Brusselaers. This is a population-based cohort study that evaluates the risk of gastric cancer among patients on long-term PPI treatment. The Authors found that long-term treatment with PPIs might be an independent risk factor for gastric cancer. Although this association has already been pointed out, the Authors did an impressive amount of work analysing and extracting data from 4 different databases. From a methodological point of view, the article seems to be correct, and I have only a few minor comments: - In the Results section: “Overall mortality was slightly lower among PPI users (17.3%) compared to H2RA maintenance users (19.4%)…” was this difference significant? - The Authors include patients from 2005 to 2012, plus an extra two years of follow up. Since the article is under review in 2017, it might be worth extending the analysis to more recent data, as the consumption of PPIs is increasing over the years. - Among the inclusion criteria, reported in the design section, the Authors state that “The study cohort included all Swedish residents who received AT LEAST one dispensed prescription of commonly prescribed drugs…”, however in the flowchart patients were excluded because only one prescription of PPIs or H2RAs. Please clarify this aspect. Some of the results are quite unexpected, In particular the markedly increased risk among individuals younger than 40 years of age. The authors possibly relate this to the increase of atrophic gastritis and obesity in the country, although probably other factors also need to be taken into consideration. Moreover, a higher risk was also found in patients taking medication for less than 1 year, and this is consistent with the fact that most gastric cancers are usually detected within one year after onset of symptoms. Finally, as for most studies on side effects of long term PPI treatments, the main problem is that the majority of patients taking PPIs usually have more co-morbidities or risk factors compared to the control groups/general population, and that could be the cause of most side effects. Indeed, the main problem of this type of studies is the high risk of potential confounders and biases that can affect the analyses. The Authors correctly recognise these limits and problems in the discussion of their manuscript. Small typo in the “article summary strengths and limitations of this study”: indication

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Reviewer Name: Helge L. Waldum
Institution and Country: Department of Gastroenetrology and Hepatology, St.Olavs Hospital, Trondheim, Norway
Competing Interests: None

In the present epidemiological study based upon Swedish registers the authors found increased frequency of gastric cancers in patients having been taking PPIs for at least six months during a 7 year period. The strength of the study is the large sample, the robustness of the registers and consistency of the results in subgroups and the total material. It is notable that the increase in gastric cancer is particularly marked in young patients. In this context it should be recalled that gastric cancers of diffuse type in contrast to the intestinal type s not in decline and in US even has been reported to be increased in young people. The authors suggest that obesity causing gastritis could be the cause of the increase in young persons. This is at best speculative.

>> Response: We agree that the age-effect we found is indeed intriguing and may be related to the increased risk of gastric cancer among young individuals. We added the following paragraph to the discussion: “Increasing risks of gastric cancer in young populations have been described previously, in particular of the diffuse type of gastric adenocarcinoma. (24, 25) Gastric symptoms in this group are also often over-looked, leading to a widespread (uncontrolled) use of PPIs.(25) Additionally, gastric carcinogenesis may be accelerated in younger patients (who also have a higher likelihood of a family history of gastric cancer),(26) which may in turn contribute to a higher vulnerability to PPI’s potentially harmful effects. A further exploration into the presence and severity of gastrointestinal risk factors, age-specific effects and potential mechanistic pathways is warranted.” We also changed the wording in the sentence referring to the potential underlying mechanism from “may” to “might”.

Table 3 showing lower increase in risk the longer the patient had taken PPI is difficult to understand and in some way makes it difficult to accept the total results?

>> Response: Since PPIs are often administered for known risk factors for gastric cancer (e.g. peptic ulcers, H. pylori), it is not entirely surprising that the risk seems to go down over time. Therefore, especially the analyses in groups without known risk factors are of interest, since these also show increased risks of gastric cancer. We adapted the discussion part on this topic as follows: “The seemingly decreasing risk estimates fact that the risk seems to go down with a longer-duration of use is probably because PPI is beneficial for most individuals with known risk factors for cancer (e.g. peptic ulcers, H. pylori) – yet further research seems needed for those on maintenance therapy without gastrointestinal indications (e.g. aspirin and NSAIDs users).”

Moreover, gastric cancer is primarily a disease of older people, so it is remarkable that PPIs should induces gastric cancer after such a short period? It should be recalled that gastric carcinoids (no called gNETs) and gastric cancer first developed after more than 20 years in persons borne with defect protonpump due to a mutation (Calvete et al. Human Mol Genet 2015; 24:2914-2922).

>> Response: We acknowledge that this is indeed an unexpected finding, together with the very high risk among young people who were unlikely to be exposed to PPIs for decades. Some people may be more vulnerable to carcinogenic effects related to PPI than others, based to their underlying indication, genetics, or even micrbiome (e.g. prior antibiotic use).

We elaborated more on the mechanistic pathways (see below) and added the following to the discussion “The impact of these proposed underlying mechanisms may also be person- and time-dependent, which could explain why PPIs are seemingly more harmful in the younger age groups.”

Furthermore, this manuscript does not mention animal studies. It has been known for more than 30 years that profound inhibition of gastric acid secretion in rodents induces gastric tumours of variable malignancy (Havu N. Digestion 1986; 35(Suppl.1):42-55 and Poynter D et al. Gut 1985; 26:1284-1293).
Secondary hypergastrinemia leading to ECL cell hyperplasia has been accepted as the mechanism for tumourigenic effect. ECL cell differentiation in human gastric carcinomas has been described in gastric carcinomas in general (Waldum et al. Cancer 1998; 83; 435-444) and in the signet ring subtype in particular (Bakkelund K et al. J Histochem Cytochem 2006; 54: 615-621). These facts should be taken into the discussion. In general, the mechanisms of PPIs carcinogenic effect should be discussed.
Nevertheless, this study should be accepted after corrections, due to the widespread use of PPIs and the consistent finding in this study.

>> Response: Thank you for your suggestions. We added the suggested references, and the following text to the discussion: “Already 30 years ago, animal studies showed that profound inhibition of gastric acid secretion in rodents induces gastric tumours, with secondary over-stimulation (hypergastrinemia) leading to enterochromaffin-like cell (ECL) hyperplasia as generally accepted mechanism of this carcinogenic effect.(25, 26) ECL differentiation has also been described in human gastric carcinomas, particularly in the signet ring subtype.(27, 28)” and “Long-term PPI use has also been linked to the development of fundic gland polyps.(32)”

Reviewer: 2
Reviewer Name: Dr. Leonardo Henry Eusebi
Institution and Country: Department of Medical and Surgical Sciences, University of Bologna, Italy
Competing Interests: None declared

I read with interest the work by Brusselaers. This is a population-based cohort study that evaluates the risk of gastric cancer among patients on long-term PPI treatment.
The Authors found that long-term treatment with PPIs might be an independent risk factor for gastric cancer. Although this association has already been pointed out, the Authors did an impressive amount of work analysing and extracting data from 4 different databases.

Comment: From a methodological point of view, the article seems to be correct, and I have only a few minor comments:

Response: Thank you for the constructive feedback. Please find our specific answers below.

Comment: In the Results section: “Overall mortality was slightly lower among PPI users (17.3%) compared to H2RA maintenance users (19.4%)…” was this difference significant?

Response: We did perform a chi-square test, and because of the large number of participants, it is not surprising that this is indeed statistically significant ($p<0.001$). The p-value for the non-significant difference in gastric cancer mortality is now also added to the manuscript ($p=0.782$), as well as a short sentence in the methods that the Chi-squared test was used to calculate these.

Comment: The Authors include patients from 2005 to 2012, plus an extra two years of follow up. Since the article is under review in 2017, it might be worth extending the analysis to more recent data, as the consumption of PPIs is increasing over the years.

Response: We do not have the more recent data at this point, and it would take at least 1 year to get newer data because of currently large queues to get data from the Swedish National Board of Health and Welfare which maintains and updates the data. The Swedish Cancer Registry has a delay of 1-2 years in registration, so would maximally be able to include up to 2015 if we would be able to get the data today.

Comment: Among the inclusion criteria, reported in the design section, the Authors state that “The study cohort included all Swedish residents who received AT LEAST one dispensed prescription of commonly prescribed drugs…”, however in the flowchart patients were excluded because only one prescription of PPIs or H2RAs. Please clarify this aspect.

Response: The total source cohort includes every individual in Sweden with at least 1 prescription of any of these commonly-prescribed drugs, which does cover almost the entire Swedish population. Yet, our main defining criterion for the exposure to PPI/H2RA use was the minimal cumulative dosage of 180 days. We clarified this in the methods section, so that “the source cohort included all Swedish residents….” Instead of “the study cohort …”

Comment: Some of the results are quite unexpected, In particular the markedly increased risk among individuals younger than 40 years of age. The authors possibly relate this to the increase of atrophic gastritis and obesity in the country, although probably other factors also need to be taken into consideration. Moreover, a higher risk was also found in patients taking medication for less than 1 year, and this is consistent with the fact that most gastric cancers are usually detected within one year after onset of symptoms.

Response: We added the following sentence to the discussion (also in response to the other reviewer): “(23) Increasing risks of gastric cancer in young populations have been described previously, in particular of the diffuse type of gastric adenocarcinoma. (24, 25) Gastric symptoms in this group are also often over-looked, leading to a widespread (uncontrolled) use of PPIs.(25) Additionally, gastric carcinogenesis may be accelerated in younger patients (who also have a higher likelihood of a family history of gastric cancer),(26) which may in turn contribute to a higher vulnerability to PPI’s potentially harmful effects. A further exploration into the presence and severity of gastrointestinal risk factors, age-specific effects and potential mechanistic pathways is warranted.” The issue of reverse causality was discussed as follows: “The problem of reverse causality, i.e. individuals taking PPIs because of symptoms arising from an undetected cancer, should have been reduced by only including individuals with at least 180 days (6 months) of cumulative exposure before any cancer diagnosis. In addition, we excluded all individuals who had gastric cancer within a year after inclusion and also stratified the analyses by duration of use; which still showed increased risks (respectively SIR=1.61 and SIR=2.19 among those with an exposure duration between 1 and 3 years). These increased risks may not be entirely explained by reverse causality and detection bias alone – since most cases of gastric cancer are believed to be detected within 1 year after onset of symptoms.”

Comment: Finally, as for most studies on side effects of long term PPI treatments, the main problem is that the majority of patients taking PPIs usually have more co-morbidities or risk factors compared to the control groups/general population, and that could be the cause of most side effects. Indeed, the main problem of this type of studies is the high risk of potential confounders and biases that can affect the analyses. The Authors correctly recognise these limits and problems in the discussion of their manuscript.

Response: Yes, we do recognise these limits and problems in the discussion section of the manuscript.

Comment: Small typo in the “article summary strengths and limitations of this study”: indication

Response: Corrected

VERSION 2 – REVIEW

REVIEWER	Helge L. Waldum Norwegian University of Science and Technology, Trondheim, Norway
REVIEW RETURNED	01-Sep-2017

GENERAL COMMENTS	An important study which now is acceptable for publication